REMARKS/ARGUMENTS

Claims 24-40 are pending in the application.

Claims Rejection - 35 U.S.C. § 101. On page 2 of the Detailed Action, last paragraph, it is stated that claims 24-40 are rejected under 35 U.S.C. § 101 as not supported by either a specific asserted utility or a well-established utility for reasons advanced in the last office action. However, on page 3 of the Detailed Action, it is stated (last two sentences) that "[t]hus the invention provides a structurally defined library directed to reverse turn structures, which are well recognized as common biological binding motifs. In view of the statement above, the 101 rejection no longer applies." Applicant thus understands that the 35 U.S.C. § 101 rejection (which was interposed as to claims included in 1-24 and now canceled) has been withdrawn, and that there is no pending section 101 rejection. If Applicant has misunderstood the Detailed Action, Applicant requests that the next action clarify the position of the Office, and that the next action not be final.

Claims Rejection - 35 U.S.C. § 112, First Paragraph. Claims 24 -40 are rejected as failing to comply with the written description requirement. The separate arguments advanced are individually discussed below.

A) It is asserted that the as-filed specification does not disclose the definitions of R_1 - R_7 as being each independently hydrogen or that each constituent metallopeptide library member varies by at least one of R_1 - R_7. At page 22, lines 26-27, it is stated that the functional R groups "may be side chains of amino acids." Glycine is an amino acid; its side chain is hydrogen. That hydrogen is intended to be included may be seen at numerous instances with the specification: see, e.g., page 13, lines 27-30, discussing sequences such as Gly-Gly-Cys; page 18, line 21, defining "Bbb" as including Gly; and, page 32, Example 11, lines 10 and Example 12, line 29.

With respect to "varies by at least one of R_1 - R_7, on pages 22-23 of the specification, the library members are discussed. This provides at length that different functional groups may be utilized. See

page 22, lines 20-24. See also page 4, lines 33-34 (the "unique selection or sequence of amino acid residues" is a result of varying by at least one of R_1 - R_7 in claim 24). See also page 8, line 8 ("distinct, unique and different amino acid sequences"); and page 8, line 23.

It is further asserted that the as-filed specification discloses an orthogonal protecting group, and claim 40 provides that a reactive sulfur atom in any one or more R groups is protected by a non-orthogonal sulfur atom-protecting group. This is disclosed, e.g., at page 5, lines 25-30:

> In this library and the other libraries provided above, the members may include a sequence with at least one amino acid residue or mimic of an amino acid residue containing at least one sulfur atom in which the sulfur atom is protected by a non-orthogonal S-protecting group. In this library and the other libraries provided above, the orthogonal S-protecting group may be removed without removing the non-orthogonal S-protecting group.

See also Examples 18 and 19, pages 36-38, discussing specific methods for selective deprotection of sulfurs by means of both an orthogonal S-protecting group and protecting groups that are not orthogonal. See also as-filed claim 10.

B) It is asserted that the specification does not provide a detailed description "wherein each of the variables comprises any type of functional group." There are two specific objections raised. At the bottom of page 6 of the Detailed Action, it is stated that "cys can react with each other in a given library or cross-link with other cys in other libraries." As a general statement, this is true. However, it is central to the invention that both orthogonal and non-orthogonal protecting groups for the reactive sulfur in cys are provided to avoid just this eventuality. See, e.g., page 8, lines 17-22, discussing as an object of the invention "to provide methods for synthesis of peptides wherein the peptides contain one or more reactive SH groups forming a part of a metal ion-binding domain, whereby the reactive SH groups are protected during synthesis, and are deprotected only upon complexing the peptides with a metal ion." See also the discussion under A) above with respect to use of both orthogonal and non-orthogonal S-protecting groups. Thus this invention provides compositions and methods where cross-linking and dimerization resulting from formation of disulfide bridges in cysteine residues and other residues containing a reactive sulfur may be avoid. It is also asserted that "an unequal representation of each component in the library may not result in a library having the ability to screen for the desired target." Assuming, arguendo, that this is so,

there is no requirement in patent law that any given library must have the ability to screen for any (or every) desired target. In any event, the examples provide clear guidance and direction on how the claimed invention may be employed. See, e.g., Example 5, page 26, discussing a library based on the tetrapeptide His-Phe-Arg-Trp; Example 6, pages 27-29 (same); Example 7, pages 29-30 (same); Example 10, pages 30-32, discussing library based on general structure Ac-His-Xaa-Cys-Trp-NH_2; Example 11, page 32, discussing human neutrophil elastase libraries of the general structure R-Aaa-Bbb-Cys-Val-N_2; Example 12, pages 32-33 (same); and Example 13, pages 33-34, discussing human neutrophil elastase libraries of the general structure Z-Aaa-Ser-Cys-Val-N_2.

Finally, it is further noted that claim 30 is drawn to the library "wherein the functional group is an amino acid side chain." Additionally, claim 34 is drawn to the library wherein "the combinatorial library is targeted to a known target, and at least one of R_1, R_2, R_3, R_4, R_5, R_6, or R_7 is a side chain of a peptide that binds to the known target."

Claim Rejection - 35 U.S.C. § 103. Claims 24-40 are rejected under 35 U.S.C. § 103 as unpatentable over Sharma, U.S. 6,027,711. Claim 24 is amended to include the limitation of claim 37, now canceled, that "the sulfur atom (S) is protected by an orthogonal sulfur atom-protecting group compatible with peptide solid phase synthesis and removable without cleaving the peptide from solid phase."

It is asserted that the instant application was, at the time the invention was made, commonly owned with U.S. 6,027,711, and accordingly rejection is not proper pursuant to section 103(c). While the section 103 rejection does not specify the applicable subsection of section 102, it is clear that only subsection 102(e) would be applicable (e.g., not subsections 102(a) or (b)). Pursuant to MPEP § 706.02(l)(3), a statement that the application and reference were, at the time the invention was made, owned by the same entity is made below under the heading "Statement Concerning Common Ownership." Accordingly, the '711 patent is not available as prior art.

Additionally, the ground of rejection asserts that specific protecting groups such as S-aminopropyl cysteine or S-aminoethyl cysteine are "covered by the broad claimed orthogonal protecting groups." There is no disclosure or suggestion in the '711 patent that these specific protecting groups can be removed to result in a reactive -SH group. The only disclosure of either S-aminopropyl cysteine or S-aminoethyl cysteine is as a "basic residue" which may be employed (see column 38, lines 63-67 and column 39, lines 10-14), and which may in some instances contribute a nitrogen (N) to binding (see column 37, lines 57-61 and column 38, lines 63-67). There is no teaching or suggestion that either residue may be deprotected such that it contributes a sulfur (S) for binding. Indeed, the specific teaching at columns 37-39 disclose, in each instance, a different position for a residue that contributes an S for binding (see, e.g., the description of Ccc at column 37, line 65 bridging column 38, line 3).

Claims 24-40 are rejected under 35 U.S.C. § 103 as unpatentable over Hnatowich et al. (U.S. 5,980,861). Hnatowich does not disclose libraries synthesized by use of orthogonal sulfur atom-protecting groups as defined in the specification. The term is defined at page 14, line 20 bridging page 16, line 18, and specifically at page 14, starting at line 20:

> The SH protecting group is chosen such that (a) the synthesis of peptide derivatives with S-protecting group is compatible with methods of solution and solid phase peptide synthesis, so that the S-protecting group is stable during synthetic procedures, and (b) the S-protecting group can be deprotected in situ, without cleavage from the resin in the case of solid phase synthesis, during the metal complexation step.

In addition, claim 24, as amended, contains a specific limitation, "wherein each constituent metallopeptide library member is made by a synthetic process wherein the sulfur atom (S) is protected by an orthogonal sulfur atom-protecting group compatible with peptide solid phase synthesis and removable without cleaving the peptide from solid phase." To the extent that the prior Office Action suggests that Fmoc may be an orthogonal sulfur-protecting group, Applicant asserts that Fmoc is an amino protecting group, not a sulfur protecting group. While it is certainly well known that Fmoc may be employed in peptide synthesis, Fmoc was discussed in the prior Amendment to demonstrate that the S-acetyl thioester group employed by Hnatowich is <u>not</u> compatible with peptide synthesis, because piperidine, which is commonly used to cleave Fmoc groups from amino functions during peptide synthesis, would also hydrolyze a thioester

bond. Thus the S-acetyl thioester group employed by Hnatowich is not an "orthogonal sulfur protecting group" as defined by Applicant.

Statement Concerning Common Ownership. As the Office Action notes, both the instant application and co-pending application 09/483,837 are commonly assigned (Detailed Action at page 11). Pursuant to MPEP § 706.02(l)(3), the undersigned attorney of record for Applicant states:

The instant application number 09/883,069 and co-pending application 09/483,837 were, at the time the invention of instant application number 09/883,069 was made, owned by Palatin Technologies, Inc. The parent of co-pending application 09/483,837 (issued as U.S. Patent No. 6,027,711, with 09/483,837 being a divisional thereof) is shown as owned by RhoMed Incorporated; since June 25, 1996, RhoMed Incorporated has been a wholly-owned (100%) subsidiary of Palatin Technologies, Inc.

Double Patenting. It is asserted that, with the amendment to claim 24, there is no double patenting rejection with respect to co-pending application 09/483,837. Claim 24, as amended, includes the limitation of claim 37, now canceled, that "the sulfur atom (S) is protected by an orthogonal sulfur atom-protecting group compatible with peptide solid phase synthesis and removable without cleaving the peptide from solid phase." There are no claims in co-pending application 09/483,837 drawn to orthogonal protecting groups. To the extent that the Office relies upon the disclosure of specific protecting groups such as S-aminopropyl cysteine or S-aminoethyl cysteine as "covered by the broad claimed orthogonal protecting groups," Applicant respectfully traverses this ground. There is no disclosure or suggestion in co-pending application 09/483,837 that these specific protecting groups can be removed to result in a reactive -SH group. The only disclosure of either S-aminopropyl cysteine or S-aminoethyl cysteine is as a "basic residue" which may be employed (see column 38, lines 63-67 and column 39, lines 10-14 in the '711 patent), and which may in some instances contribute a nitrogen (N) to binding (see column 37, lines 57-61 and column 38, lines 63-67 in the '711 patent). There is no teaching or suggestion that either residue may be deprotected such that it contributes a sulfur (S) for binding.

Indeed, the specific teachings at columns 37-39 in the '711 patent disclose, in each instance, a different position for a residue that contributes an S for binding (see, e.g., the description of Ccc at column 37, line 65 bridging column 38, line 3 in the '711 patent).

Accordingly, even if the structures are similar, claim 24 has been amended such that it is limited to a product made by a specified process (i.e., "wherein each constituent metallopeptide library member is made by a synthetic process wherein the sulfur atom (S) is protected by an orthogonal sulfur atom-protecting group compatible with peptide solid phase synthesis and removable without cleaving the peptide from solid phase"). This is not disclosed in co-pending application 09/483,837. Accordingly, the invention of claims 24-40 are patentably distinct from the asserted claims of co-pending application 09/483,837.

Conclusion. In view of the above amendments and remarks, it is respectfully submitted that all grounds of rejection and objection have been avoided and/or traversed. It is believed that the case is now in condition for allowance and same is respectfully requested.

Also being filed herewith is a Petition for Extension of Time to December 3, 2004, with the appropriate fee. Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213. A duplicate of this paper is enclosed for accounting purposes.

Respectfully submitted,

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